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(54) Title: THERMALLY REVERSIBLE POLYURETHANE HYDROGELS AND COSMETIC, BIOLOGICAL AND MEDICAL USES			
(57) Abstract Thermally reversible polyurethane hydrogels are formed by adding water to a gel forming hydrophilic polyurethane polymer produced by reacting under anhydrous conditions an organic diisocyanate with a glycol component in an NCO/OH mole ratio of from about 0.5/1 to about 1/1 wherein the percentage by weight of the diisocyanate in the reaction mixture is from about 2 % to about 25 %. The hydrogels are solids at room temperature but liquify at higher temperatures such as body temperature and therefore are useful as carriers for the protection, delivery and sustained release of a variety of active agents including pharmaceuticals, cosmetics, living cells and organisms.			

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TERNALLY REVERSIBLE POLYURETHANE HYDROGELS AND
COSMETIC, BIOLOGICAL AND MEDICAL USES

Technical Field

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This invention relates to thermally reversible hydrogels and, in particular, to thermally reversible hydrogels produced from certain hydrophilic polyurethane polymers. The invention is also concerned with cosmetic, biological and medical applications of the polyurethane hydrogels such as carrier and delivery systems for active agents, including living cells.

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Background of the Invention

5 U.S. Patent Nos. 3,822,238 and 3,975,350
describe an active agent carrier system comprising an
active agent and as a carrier vehicle therefor, a
hydrophilic, preferably cross-linked polyurethane pol-
10 ymer. The carrier system is utilized by subjecting it
to aqueous conditions whereby the polyurethane carrier
undergoes hydration and swelling with concomitant
formation of an insoluble hydrogel from which the
active agent is leached out by and into the aqueous
medium. The rate and duration of release can be
15 controlled by employing a carrier polymer of the req-
uisite water absorptivity. Generally speaking, poly-
urethane polymers prepared from water soluble active
hydrogen resins, as exemplified by polyoxyethylene
polyols, will exhibit the highest water absorptivity.
Polymers having diminished water absorptivity can be
20 produced from less soluble resins, or by cross-
linking.

The carrier system aforesaid is useful as a
means for delivering various active agents, such as
25 medicinal or cosmetic agents, to a treatment zone.
For instance, shaped articles made of the carrier
system can be inserted into the body to provide preci-
sion administering of drugs or serums over extended
periods of time.

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Another class of hydrophilic polyurethanes that form insoluble hydrogels in the hydrated state is disclosed in U.S. Patent Nos. 4,156,066 and 4,156,067. These polyurethanes are characterized by the presence of lactone groups in the polymer backbone. The lactone may be opened by hydrolytic cleavage to form carboxylic acid groups which render the polymer soluble in alkaline medium. Other specialized hydrophilic polyurethanes are the polyurethane diacrylates of U.S. Patent No. 4,359,558 and the polyurethane quaternary ammonium salts of U.S. Patent No. 4,451,635.

Description of the Invention

An active agent carrier vehicle utilizing hydrophilic polyurethane polymers has now been discovered which differs in its composition and mode of operation from the polyurethane polymer carrier vehicles heretofore, and the provision of said polyurethane polymer carrier vehicles herein and active agent carrier systems produced therefrom constitute the principal object and purpose of the invention. Other objects and purposes will become manifest in the ensuing description.

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5 The active agent carrier vehicle of the invention is a thermally reversible hydrogel comprising water and a gel-forming, hydrophilic polyurethane polymer which is produced by reacting under anhydrous conditions an organic diisocyanate with a glycol component comprising a polyoxyethylene glycol or mixture of glycols in an NCO/OH weight ratio of from about 0.5/1 to about 1/1 and wherein the percentage by weight of the diisocyanate in the anhydrous reaction mixture exclusive of catalyst is from about 2% to about 25%, preferably from about 5% to about 17%.

15 "Anhydrous" as used in this specification means that the reaction mixture is sufficiently free of water so that the polymer product will be thermally reversible between a gel state and a sol state as further described below. Anhydrous conditions may be produced in any known manner of providing a dry reaction environment. Typical drying procedures include
20 subjecting reactants to heat, vacuum, azeotropic distillation or contact with dessicating agents. Drying of the glycol component is especially important since glycols commonly contain residual moisture, often in amounts sufficient to deleteriously affect the properties of the herein gel compositions. The dried glycols, which tend to be hygroscopic, should be protected from atmospheric moisture. Other reactants, i.e.,
25 isocyanates and catalysts, can ordinarily be used without drying, owing to their lack or near lack of

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associated moisture. Precautions should also be taken to ensure that all reaction vessels and apparatus are free of moisture.

5 It is, of course, possible that extremely small or trace amounts of moisture may still be present in the reaction mixture. However, by employing the usual drying techniques such as above described, it has been found that anhydrous conditions suitable
10 for practice of the invention can be realized.

 In preparing the thermally reversible hydrogel of the invention, the polyurethane polymer component, preferably granulated or in small pieces, is
15 added to an aqueous medium such as water or an aqueous solution. The resulting mixture is allowed to stand until the polymer undergoes hydration and concomitant swelling. This generally takes about one to four hours, depending on the particular polymer and its
20 state of subdivision.

 The aqueous medium containing the swollen polymer is then heated at mildly elevated temperatures with vigorous agitation. Preferably, the heating is
25 conducted at temperatures of from about 37°C to about 80°C. As a consequence of this treatment, the polymer is gradually assimilated into the aqueous medium. At this point, heating and stirring are discontinued. By way of analogy to the gel (or hydrogel) and sol states

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of colloidal dispersions, the resulting liquid may be described as the sol state of the thermally reversible hydrogels of the invention. No necessary limitation to colloidal character is intended, however, since the
5 sol state of the polymer in some respects appears to behave more like a true solution than a colloidal dispersion.

So far as can be ascertained, the assimila-
10 tion of the polyurethane polymer into the aqueous medium involves both dissolution and dispersion of the polymer. As the temperature of the sol is lowered, it is believed that aggregation of the polymer particles occurs with ensuing reversion to the gel state. But
15 whatever the mechanism of the sol/gel transition, the aqueous polyurethane polymers of the invention constitute a thermally reversible sol/hydrogel-type system.

The temperature at which the sol reverts to
20 the gel and vice versa will depend on the particular polyurethane polymer and its concentration in the aqueous medium. Hydrogels have been obtained after equilibration in which the sol/gel transition occurs in the temperature region of about 30°C to about 45°C.
25 In general, the concentration by weight of the polymer component in the hydrogel is about 1% to about 15%, preferably about 3% to about 7%.

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The polyurethane polymer used in forming the thermally reversible hydrogels of the invention is prepared by the reaction of the diisocyanate and glycol component(s) in the presence of a catalyst for the polyurethane reaction. Suitable catalysts include tin salts; organic tin esters as exemplified by dibutyl tin dilaurate; tertiary amines of which triethyl diamine (DABCO) and N,N,N',N'-tetramethyl-1,3 butane diamine are representative, as well as other known catalysts for such reaction. As indicated above, to insure anhydrous conditions the glycol component is freed of moisture prior to reacting it with the diisocyanate. Drying is conveniently effected by heating the glycol component in vacuo (8 mm of Hg or less absolute) at mildly elevated temperatures, typically about 50°C to about 70°C.

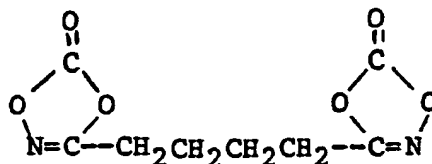
In carrying out the polyurethane reaction, the moisture-free glycol component, diisocyanate and catalyst are brought together at about room temperature or slightly higher but usually not above about 60°C. Where more than one glycol is used, these are preferably formed into a homogeneous mixture or melt before reacting with the diisocyanate. Following mixing of the glycol and diisocyanate components in the presence of the catalyst, a mildly exothermic reaction occurs, the temperature rising to about 50°C

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to 80°C after which the reaction is completed by heating the mixture in the range of about 80°C to 110°C.

Representative commercial polyoxyethylene glycols are CARBOWAX® 1450, CARBOWAX® 4500 and CARBOWAX® 8000 in which the numbers refers to number average molecular weights. These products are manufactured by Union Carbide Corporation.

Representative diisocyanates are methylene-bis(cyclohexyl-4,4'-isocyanate), trimethyl hexamethylene diisocyanate, isophorone diisocyanate, cyclohexyl diisocyanate and diisocyanate precursors or equivalents such as the nitrile carbonates, e.g., the adiponitrile carbonate of the formula:



In preparing the polyurethane polymer constituent of the herein hydrogels, the molecular weight (in the case of glycols, hereinafter number average molecular weight) of the glycol component such as polyoxyethylene glycol must be such that the stated

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diisocyanate percentage and NCO/OH mole ratio is preserved in the reaction mixture. Thus, in a polyurethane formulation containing by weight 10% of diisocyanate and 90% glycol and an NCO/OH mole ratio of 1/1, the glycol will have a molecular weight that is about 9 times the molecular weight of the diisocyanate. If the diisocyanate aforesaid is methylenebis(cyclohexyl-4,4'-isocyanate), which has a molecular weight of 260, then the molecular weight of the glycol will be 9 times 260 or 2340. Glycol molecular weights for other diisocyanate percentages and NCO/OH mole ratios are computed in like manner.

Preferably, the glycol component is a blend of a lower polyoxyethylene glycol (sometimes referred to as an "alkylene glycol") with a higher member in which the average molecular weight of the glycol blend satisfies the NCO/OH ratio and diisocyanate percentage. Thus, a glycol blend consisting of 1 mole each of CARBOWAX® 1450 and diethylene glycol M.W. 106.12 would have an average molecular weight of $(1450 + 106.12/2)$ or 778. Average molecular weights for other mole ratios of glycols are computed similarly. Generally, the glycol blend will contain a lower alkylene glycol such as diethylene or triethylene glycol and a higher polyoxyethylene glycol having an average molecular weight up to about 10,000. An especially preferred glycol blend is a mixture of up to about 95% diethylene glycol and up to about 5% of one or more

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polyoxyethylene glycols having an average molecular weight in the range of from about 1450 to about 8000.

5 Generally speaking, high viscosities are encountered when incorporating into the aqueous medium a polyurethane polymer prepared from a polyoxyethylene glycol having a molecular weight approaching 14,000. On the other hand, a polyurethane polymer prepared from a glycol having a molecular weight below about 10 1450 gives hydrogels that have low viscosities. However, blending the high molecular weight polyoxyethylene glycol with diethylene glycol as above described reduces the viscosity during mixing of the resulting polyurethane polymer with an aqueous medium and produces a satisfactory hydrogel. Blending di- 15 ethylene glycol with a lower molecular weight polyoxyethylene glycol also produces a satisfactory hydrogel having good gel properties.

20 The thermally reversible hydrogels of the invention provide a highly effective means for the protection, controlled delivery and sustained release of an active agent. To this end, the hydrogel is melted to the liquid state and the active agent is 25 mixed with the liquid. The temperature of the mixture is then lowered to promote gelling. The active agent is thereby encapsulated in the gel matrix and thus immobilized and protected. On melting the gel, the active material is rendered mobile in the fluidized

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hydrogel for delivery and application to the treatment area at a rate dependent on its concentration in the gel, the rate at which the gel melts, and other factors such as the environment in which melting occurs. Active agents may also be first dispersed in an aqueous medium used to form the gel state of the polyurethane, thereby being incorporated into the hydrogel during formation thereof.

It can thus be seen that the mechanism whereby the active agent is released from the hydrogel of the invention differs in its mode of operation as compared to leaching of the active agent from the water insoluble, water swellable polyurethane polymers of the cited patents.

Representative active agents, which can be applied singly or in combination by means of the polyurethane hydrogels of the invention, are pharmaceuticals including anti-cancer drugs; agrichemicals including pesticides of all types such as bacteriocides, viricides, insecticides, herbicides, larvicides, fungicides, algacides and nematocides; topical or dermatological agents such as deodorants, cosmetics, protective screens such as ultraviolet skin coatings, moisturizers and the like; and a host of other substances such as salts, pH regulators, hormones, enzymes and other proteinaceous substances, fragrances, deodorants, humectants, antioxidants, pre-

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servatives, and food additives such as flavors, essences and spices.

5 The hydrogels are also useful as non-toxic culture media for the growth of microorganisms and as gel matrices for the immobilization of enzymes, bacterial cells or other microorganisms in carrying out fermentation reactions such as the manufacture of citric acid. In this specification the term "living
10 cells" is intended to mean and include individual animal and plant cells as well as cell clusters, tissues, organs and organisms including microorganisms such as bacteria, molds and fungi. Furthermore, the hydrogels of the invention can also function as non-
15 toxic media for electrophoretic separation of biological substances such as enzymes, viruses, proteins and nucleic acids in accordance with well known techniques.

20 In the field of medicine, the hydrogels are useful in a method developed for the treatment of tumors. In this method, the thermally reversible polyurethane in gel form and containing an anti-cancer drug is applied to or at the site of a tumor. The
25 tumor is then subjected to a source of radiant heat such as a diathermy machine. When the temperature of the tumor reaches the point at which the gel becomes fluid, the entrapped drug is released and brought into contact with the tumor. An unexpected and beneficial

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result is that the combined action of the drug and the heat developed by radiation exert a synergistic effect, thereby enhancing the therapy.

5 In cosmetic applications, such as in the preparation of face masks, wrinkle creams, mascara bases, dry-skin protectants, and the like, the hydrogels are substituted for or used in addition to the gelatinous substances commonly present in such formulations.
10

 The following non-limiting examples will further illustrate the invention. In the examples, all parts are by weight unless specified otherwise.
15

EXAMPLE 1 - CELL CULTURING

 A polyether moiety is prepared by mixing
20 81.4 parts of CARBOWAX® 4500 polyoxyethylene glycol (Union Carbide Corporation) and 4.1 parts of diethylene glycol with stirring at 70°C to form a homogeneous melt. The resulting glycol mixture is then subjected to vacuum in order to remove moisture. While
25 continuing the stirring, 14.5 parts of DESMODUR W® diisocyanate [(methylenebis(cyclohexyl-4,4'-isocyanate), Mobay Chemical Corp.] are added. When the temperature decreases to 50°C, 0.1 part of T₁₂ catalyst (dibutyl tin dilaurate, Air Products and Chemicals,

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Inc.) is added and the mixture allowed to exotherm to about 70°C. The reaction mass is then poured into a polypropylene pan. During pouring, the temperature of the mass continues to rise and, as the temperature approaches 80°C, the mass foams. Upon completion of the pouring operation, the pan is placed in an air circulating oven at 100°C and maintained in the oven for one hour to cure the polymer.

After cooling to ambient room temperature, the polymer mass is cut into small pieces. A sufficient amount of the small pieces is mixed with water to form a mixture containing 12% solids. The mixture is stirred while increasing the temperature of the mixture to 95°C. With continued stirring, the mass begins to homogenize and then thickens. Upon cooling to 55°C, the mass sets into a highly viscous gel. If desired, lower solids concentration hydrogels may be formed by dilution with water or with an aqueous culture medium. For storage purposes, the hydrogel may be dried.

Hydrogels of any desired solids content and of any desired aqueous consistency may be prepared by mixing the required amount of the dry polymer with water and/or an aqueous medium such as a culture medium, and heating the mixture to about 40°C with stirring. A hydrogel containing 5% of the above-described polymer with an aqueous culture medium is in

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its sol state, i.e., a flowable, somewhat syrupy liquid at 37°C. But when cooled to room temperature (20°C - 22°C), the mixture sets into a solid gel and thus can be used as an agar substitute for the culturing of cells and organisms. The liquid hydrogel may be brought to the desired pH for specific cells or microorganisms (such as E. coli) by the addition of a buffer solution or a dilute acid or alkaline solution.

EXAMPLE 2 - TUMOR TREATMENT

To 81.4 parts of CARBOWAX® 4500 polyethylene glycol having a number average molecular weight of 4500 is added with mixing 4.1 parts of diethylene glycol. The mixture is heated to 60°C to 65°C to form a homogeneous melt which is placed under vacuum until all traces of moisture are removed.

While stirring, 14.5 parts of DESMODUR W® diisocyanate are added to the mixture. The temperature of the mixture drops. When it reaches about 50°C, 0.2 part of T₁₂ catalyst is added. The mixture then starts to exotherm. When the temperature reaches 73°C to 75°C, the mixture is poured into a polypropylene tray, the tray is placed in a circulating oven and the polymer cured at 100°C for one hour. The resulting compact slab or polymer is cut into small pieces, using a granulator.

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Bleomycin sulfate (an anti-cancer drug) is dissolved in physiological saline at 100 ppm concentration. The granulated polymer is placed in the saline with the drug, 7 parts polymer per 93 parts of the saline, and the polymer allowed to swell for three hours.

After this period, the temperature of the polymer-saline system is slowly raised to 75°C to 76°C under vigorous stirring. The polymer dissolves and forms a homogeneous solution. The solution is slowly cooled under constant stirring to 35°C to 36°C, when the stirring is discontinued and the mixture allowed to gel.

The gel remains solid at temperatures up to 37°C to 38°C, even in water or physiological saline, and releases the entrapped drug only slowly. When heated to 45°C, the gel melts and releases the entrapped drug rapidly. Thus, it is suitable as a carrier for anti-cancer and other drugs, which can be placed at the tumor site or a site of infection and released during hyperthermia; that is, when the site is overheated to 45°C.

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EXAMPLE 3 - COSMETIC USES

5 In a suitable vessel, 32.0 parts of CARBOWAX® 1450, 52.7 parts of CARBOWAX® 8000, and 2.5 parts of diethylene glycol are mixed and heated to 65°C. Vacuum is applied to the heated mixture until all traces of moisture are removed.

10 To the heated mixture is added 12.7 parts of DESMODUR W®. When the temperature falls to 45°C to 48°C, 0.15 part of T₁₂ catalyst is added under constant stirring. The mixture starts to exotherm. When the temperature reaches 70°C, stirring is discontinued and the mixture poured into a polypropylene tray. The
15 tray is placed in a circulating oven and the mixture cured for one hour at 100°C.

20 The solid block of polymer is granulated to 1/4-inch particles. A gel is prepared therefrom containing 25% solids, following the procedure of Example 1. The solvent in this case is 85 parts of distilled water and 15 parts of SDA ethyl alcohol. The gel has a viscosity of 1,200 cP at 25°C, and is used for
25 preparation of face masks, wrinkle creams and as a base for mascara.

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EXAMPLE 4 - SKIN PROTECTANT

In a suitable vessel, 79.3 parts of CARBOWAX® 8000 and 5.4 parts of diethylene glycol are melted together at 65°C and vacuum is applied to remove moisture. 15.3 parts of DESMODUR W® and 0.2 part of catalyst T₁₂ are then added. The mixture exotherms and is poured into a polypropylene tray. The tray is placed in a circulating oven and the mixture cured at 90°C for 1.5 hours. The resulting polymer is then granulated into 1/4-inch size pellets.

A gel is prepared from 5 parts of the polymer and 95 parts of water, following the procedure described in Example 1. The gel is easily spreadable on the skin, where it forms an invisible, nongreasy and nontacky film, usable as skin protection for dry skin, psoriasis, etc. The film is easily removed with warm water.

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CLAIMS:

- 5 1. A thermally reversible hydrogel comprising water and a gel forming hydrophilic polyurethane polymer produced by reacting under anhydrous conditions an organic diisocyanate with a glycol component comprising a polyoxyethylene glycol or mixtures of glycols in a mole weight ratio of NCO/OH of from about 0.5/1 to about 1/1 and wherein the percentage by
10 weight of the diisocyanate in the reaction mixture is from about 2% to about 25%.
- 15 2. The hydrogel of Claim 1 wherein the percentage by weight of the diisocyanate is from about 5% to about 17%.
- 20 3. The hydrogel of Claim 1 wherein the concentration by weight of the polyurethane polymer is from about 1% to about 15%.
- 25 4. The hydrogel of Claim 1 wherein the concentration of the polyurethane polymer is from about 3% to about 7%.

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5. The hydrogel of Claim 1 wherein the glycol component is a mixture of a lower glycol and a polyoxyethylene glycol having a number average molecular weight up to about 10,000.

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6. The hydrogel of Claim 5 wherein the glycol component is a mixture of diethylene glycol and at least one polyoxyethylene glycol having a number average molecular weight of from about 1450 to about 8000.

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7. The hydrogel of Claim 1 wherein the diisocyanate is selected from the class consisting of methylenebis(cyclohexyl-4,4'-isocyanate), trimethyl hexamethylene diisocyanate, isophorone diisocyanate and cyclohexyl diisocyanate.

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8. The hydrogel of Claim 7 wherein the diisocyanate is methylenebis(cyclohexyl-4,4'-isocyanate).

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9. The hydrogel of Claim 6 wherein the glycol component is a mixture of diethylene glycol and a polyoxyethylene glycol having a number average molecular weight of about 1450.

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10. The hydrogel of Claim 6 wherein the glycol component is a mixture of diethylene glycol and a polyoxyethylene glycol having a number average molecular weight of about 4500.

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11. The hydrogel of Claim 6 wherein the glycol component is a mixture of diethylene glycol and a polyoxyethylene glycol having a number average molecular weight of about 8000.

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12. The hydrogel of Claim 6 wherein the glycol component is a mixture of diethylene glycol, a polyoxyethylene glycol having a number average molecular weight of about 1450 and a polyoxyethylene glycol having a number average molecular weight of about 8000.

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13. An active agent carrier system comprising an active agent and as the carrier vehicle therefor a hydrophilic, thermally reversible hydrogel comprising water and a gel forming polyurethane polymer produced by reacting under anhydrous conditions an organic diisocyanate with a glycol component comprising a polyoxyethylene glycol or mixture of glycols in a mole weight ratio of NCO/OH of from about 0.5/1 to

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about 1/1 and the percentage by weight of the diisocyanate in the reaction mixture is from about 2% to about 25%.

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14. The carrier system of Claim 13 wherein the percentage of the diisocyanate is from about 5% to about 17%.

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15. The active agent carrier system of Claim 13 wherein the active agent is a pharmaceutical.

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16. The active agent carrier system of Claim 13 wherein the pharmaceutical is an anti-cancer drug.

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17. The active agent carrier system of Claim 13 wherein the active agent is a cosmetic agent.

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18. The active agent carrier system of Claim 17 wherein the cosmetic agent is a fragrance, deodorant or mixture thereof.

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19. The active agent carrier system of Claim 13 wherein the active agent comprises living cells.

5 20. A skin protectant film produced by applying to the skin the thermally reversible hydrogel of Claim 1.

10 21. A method for the immobilization of living cells which comprises mixing the cells with the liquid form of a thermally reversible hydrogel, where-
15 in the hydrogel comprises water and a gel forming polyurethane polymer produced by reacting under anhy-
drous conditions an organic diisocyanate with a glycol component comprising a polyoxyethylene glycol or a
mixture of glycols in a mole weight ratio of NCO/OH of
20 from about 0.5/1 to about 1/1 and the percentage by weight of the diisocyanate in the reaction mixture is from about 2% to about 25%, and reducing the tempera-
ture of the liquid hydrogel to convert it to the solid gel state, thereby immobilizing the cells in the gel
matrix.

25 22. The method of Claim 21 wherein the percentage of the diisocyanate is from about 5% to about 17%.

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23. A cell delivery system comprising living cells entrapped in a thermally reversible hydrogel produced by adding an aqueous medium to a gel forming hydrophilic polyurethane polymer formed by reacting under anhydrous conditions an organic diisocyanate with a glycol component comprising a polyoxyethylene glycol or a mixture of glycols in a mole weight ratio of NCO/OH of from about 0.5/1 to about 1/1 and the percentage by weight of the diisocyanate in the reaction mixture is from about 2% to about 25%.

24. The cell delivery system of Claim 23 wherein the percentage of the diisocyanate is from about 5% to about 17%.

25. The cell delivery system of Claim 23 wherein the water of the hydrogel is an aqueous culture medium for the cells.

26. The cell delivery system of Claim 23 wherein the amount of polyurethane polymer in the hydrogel is about 1% to about 15% by weight.

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27. The cell delivery system of Claim 23 wherein the amount of polyurethane polymer in the hydrogel is about 3% to about 7% by weight.

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28. A method of delivering an active agent to a treatment zone comprising the steps of:

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(1) mixing the active agent with a thermally reversible hydrogel in its liquid state, the said hydrogel comprising water and a hydrophilic polyurethane polymer produced by reacting under anhydrous conditions, an organic diisocyanate with a glycol component comprising a polyoxyethylene glycol or a mixture of glycols in a mole weight NCO/OH ratio of from about 0.5/1 to about 1/1 and the percentage by weight of the diisocyanate in the reaction mixture is from about 5% to about 17%;

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(2) lowering the temperature of the liquid hydrogel to convert it into the solid gel form with concomitant encapsulation therein of the active agent;

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(3) introducing the solid hydrogel containing the encapsulated active agent to the treatment zone; and

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(4) raising the temperature of the solid hydrogel to convert it to the liquid form, thereby freeing the active agent to exert its therapeutic effect at the treatment zone.

29. The method of Claim 28 wherein the hydrogel contains by weight from about 1% to about 15% of the polyurethane polymer.

30. The method of Claim 28 wherein the hydrogel contains by weight from about 3% to about 7% of the polyurethane polymer.

31. The method of Claim 28 wherein the glycol component is a mixture of a lower glycol and a polyoxyethylene glycol having a number average molecular weight of about 10,000.

32. The method of Claim 28 wherein the glycol component is a mixture of diethylene and at least one polyoxyethylene glycol having a number average molecular weight of from about 1450 to about 8000.

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33. The method of Claim 28 wherein the diisocyanate is selected from the class consisting of methylenebis(cyclohexyl-4,4'-isocyanate), trimethyl hexamethylene diisocyanate, isophorone diisocyanate and cyclohexyl diisocyanate.

34. The method of Claim 28 wherein the diisocyanate is methylenebis(cyclohexyl-4,4'-isocyanate).

35. The method of Claim 28 wherein the glycol component is a mixture of a diethylene glycol and a polyoxyethylene glycol having a number average molecular weight of about 1450.

36. The method of Claim 28 wherein the glycol component is a mixture of a diethylene glycol and a polyoxyethylene glycol having a number average molecular weight of about 4500.

37. The method of Claim 28 wherein the glycol component is a mixture of a diethylene glycol and a polyoxyethylene glycol having a number average molecular weight of about 8000.

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38. The method of Claim 28 wherein the glycol component is a mixture of diethylene glycol, a polyoxyethylene glycol having a number average molecular weight of about 1450 and a polyoxyethylene glycol having a number average molecular weight of about 8000.

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INTERNATIONAL SEARCH REPORT

International Application No. PCT/US88/00280

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC (4): C08G, 18/30; A61K, 31/00; US. CL. 528/60																	
II. FIELDS SEARCHED <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Minimum Documentation Searched ⁷</div> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 25%; border: 1px solid black;">Classification System</th> <th style="border: 1px solid black;">Classification Symbols</th> </tr> <tr> <td style="border: 1px solid black; vertical-align: top;">U.S.</td> <td style="border: 1px solid black; vertical-align: top;">528/60, 61, 66, 76 424/19, 16 428/423.1 528/903, 904</td> </tr> </table> <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸</div>			Classification System	Classification Symbols	U.S.	528/60, 61, 66, 76 424/19, 16 428/423.1 528/903, 904											
Classification System	Classification Symbols																
U.S.	528/60, 61, 66, 76 424/19, 16 428/423.1 528/903, 904																
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹ <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%; border: 1px solid black;">Category ⁹</th> <th style="border: 1px solid black;">Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²</th> <th style="width: 15%; border: 1px solid black;">Relevant to Claim No. ¹³</th> </tr> </thead> <tbody> <tr> <td style="text-align: center; border: 1px solid black;">X</td> <td style="border: 1px solid black;">US, A, 4,496,535 (GOULD) 29 JANUARY 1985</td> <td style="text-align: center; border: 1px solid black;">1-38</td> </tr> <tr> <td style="text-align: center; border: 1px solid black;">X</td> <td style="border: 1px solid black;">US, A, 4,439,585 (GOULD) 27 MARCH 1984</td> <td style="text-align: center; border: 1px solid black;">1-38</td> </tr> <tr> <td style="text-align: center; border: 1px solid black;">X</td> <td style="border: 1px solid black;">US, A, 4,235,980 (FILDES) 25 NOVEMBER 1980</td> <td style="text-align: center; border: 1px solid black;">1-38</td> </tr> <tr> <td style="text-align: center; border: 1px solid black;">X</td> <td style="border: 1px solid black;">US, A, 3,975,350 (HUDGIN) 17 AUGUST 1976</td> <td style="text-align: center; border: 1px solid black;">1-38</td> </tr> </tbody> </table>			Category ⁹	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	X	US, A, 4,496,535 (GOULD) 29 JANUARY 1985	1-38	X	US, A, 4,439,585 (GOULD) 27 MARCH 1984	1-38	X	US, A, 4,235,980 (FILDES) 25 NOVEMBER 1980	1-38	X	US, A, 3,975,350 (HUDGIN) 17 AUGUST 1976	1-38
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<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 50%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>																	
IV. CERTIFICATION <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; border: 1px solid black; vertical-align: top;"> Date of the Actual Completion of the International Search 21 MARCH 1988 </td> <td style="width: 50%; border: 1px solid black; vertical-align: top;"> Date of Mailing of this International Search Report 11 MAY 1988 </td> </tr> <tr> <td style="border: 1px solid black; vertical-align: top;"> International Searching Authority ISA/US </td> <td style="border: 1px solid black; vertical-align: top;"> Signature of Authorized Officer SAM ACQUAH </td> </tr> </table>			Date of the Actual Completion of the International Search 21 MARCH 1988	Date of Mailing of this International Search Report 11 MAY 1988	International Searching Authority ISA/US	Signature of Authorized Officer SAM ACQUAH											
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